(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 September 2001 (27.09.2001)

PCT

(10) International Publication Number
WO 01/70700 A1

(51) International Patent Classification[7]: C07D 231/06, 409/04, 401/04, A61K 31/415, A61P 25/04, 9/00, C07D 231/08

(21) International Application Number: PCT/EP01/03247

(22) International Filing Date: 22 March 2001 (22.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00201032.0 23 March 2000 (23.03.2000) EP
1014728 23 March 2000 (23.03.2000) NL

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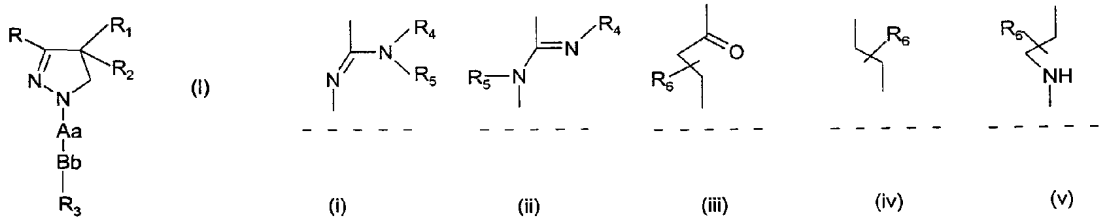
(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING CB_1-ANTAGONISTIC ACTIVITY



(57) Abstract: The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives which are potent antagonists of the cannabis CB_1-receptor. The compounds have general formula (I) wherein R and R_1 are the same or different and represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y or R and/or R_1 represent naphtyl, R_2 represents hydrogen, hydroxy, C_{1-3}-alkoxy, acetyloxy or propionyloxy, Aa represents one of the groups (i), (ii), (iii), (iv) or (v), Bb represents sulfonyl or carbonyl, R_3 represents benzyl, phenyl, thienyl or pyridyl which may be substituted with 1, 2 or 3 substituents Y or R_3 represents C_{1-8} branched or unbranched alkyl or C_{3-8} cycloalkyl, or R_3 represents naphtyl.

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4,5-Dihydro-1H-pyrazole derivatives having CB_1-antagonistic activity

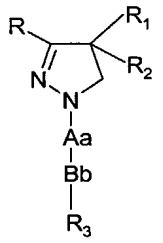
The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

The above mentioned 4,5-dihydro-1H-pyrazoles are potent Cannabis-1 (CB_1) receptor antagonists with utility for the treatment of psychiatric and neurological disorders.

Cannabinoids are present in the Indian hemp *Cannabis Sativa L.* and have been used as medicinal agents for centuries (Mechoulam, R.; Feigenbaum, J.J. *Prog. Med. Chem.* **1987**, *24*, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of Cannabinoid receptors (CB_1 and CB_2) stimulated the search for novel cannabinoid receptor antagonists (Munro, S.; Thomas, K.L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61. Matsuda, L.A.; Bonner, T.I. *Cannabinoid Receptors,* Pertwee, R.G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system. The wide distribution of CB_1 receptors in the brain, in combination with the strictly peripheral localisation of the CB_2 receptor, makes the CB_1 receptor a very interesting molecular target for CNS-directed drug discovery in the areas of both psychiatric and neurological disorders (Consroe, P. *Neurobiology of Disease* **1998**, *5*, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, *1*, 587. Greenberg, D.A. *Drug News Perspect.* **1999**, *12*, 458). Hitherto, three types of distinct CB_1 receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB_1 receptor antagonists. A representative example is SR-141716A, which is currently undergoing Phase II clinical development for psychotic disorders (Dutta, A.K.; Sard, H.; Ryan, W.; Razdan, R.K.; Compton, D.R.; Martin, B.R. *Med. Chem. Res.* **1994**, *5*, 54. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S.R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999**, *42*, 769. Nakamura-Palacios, E.M.; Moerschbaecher, J.M.; Barker, L.A. *CNS Drug Rev.* **1999**, *5*, 43). Aminoalkylindoles have been disclosed as CB_1 receptor antagonists. A representative example is Iodopravadoline (AM-630), which was introduced in 1995. AM-630 is a CB_1 receptor antagonist, but sometimes behaves as a weak

partial agonist (Hosohata, K.; Quock, R.M.; Hosohata, Y.; Burkey, T.H.; Makriyannis, A.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Life Sc.* **1997**, *61*, PL115). More recently, researchers from Eli Lilly described aryl-aroyl substituted benzofurans as selective CB_1 receptor antagonists (*e.g.* LY-320135) (Felder, C.C.; Joyce, K.E.; Briley, E.J.; Glass, M.; Mackie, K.P.; Fahey, K.J.; Cullinan, G.J.; Hunden, D.C.; Johnson, D.W.; Chaney, M.O.; Koppel, G.A.; Brownstein, M. *J. Pharmacol. Exp. Ther.* **1998**, *284,* 291). Recently, 3-alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M.; Govaerts, S.J.; Hermans, E.; Poupaert, J.H., Lambert, D.M. *Biorg. Med.Chem. Lett.* **1999**, *9,* 2233). Interestingly, many CB_1 receptor antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S.; Burkey, T.H.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Eur. J. Pharmacol.* **1997**, *334,* R1). Recent reviews provide a nice overview of the current status in the cannabinoid research area (Mechoulam, R.; Hanus, L.; Fride, E. *Prog. Med. Chem.* **1998**, *35*, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, *6*, 635. Mechoulam, R.; Fride, E.; Di Marzo, V. *Eur. J. Pharmacol.* **1998**, *359*, 1).

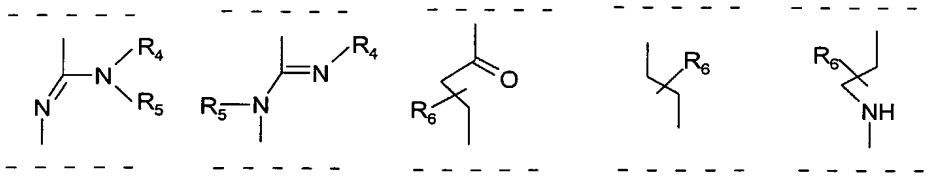
It has now surprisingly been found that the novel 4,5-dihydro-1H-pyrazole derivatives of the formula (I), prodrugs thereof, tautomers thereof and salts thereof



(I)

wherein

- R and R_1 are the same or different and represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group C_{1-3}-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C_{1-2})-amino, mono- or dialkyl (C_{1-2})-amido, (C_{1-3})-alkyl sulfonyl, dimethylsulfamido, C_{1-3}-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R_1 represent naphtyl,
- R_2 represents hydrogen, hydroxy, C_{1-3}-alkoxy, acetyloxy or propionyloxy,
- Aa represents one of the groups (i), (ii), (iii), (iv) or (v)



(i) (ii) (iii) (iv) (v)

wherein

- R_4 and R_5 independently of each other represent hydrogen or C_{1-8} branched or unbranched alkyl or C_{3-8} cycloalkyl or R_4 represents acetamido or dimethylamino or 2,2,2-trifluoroethyl or phenyl or pyridyl with the proviso that R_5 represents hydrogen
- R_6 represents hydrogen or C_{1-3} unbranched alkyl

– Bb represents sulfonyl or carbonyl,

– R_3 represents benzyl, phenyl, thienyl or pyridyl which may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, or R_3 represents C_{1-8} branched or unbranched alkyl or C_{3-8} cycloalkyl, or R_3 represents naphtyl

are potent and selective antagonists of the cannabis CB_1-receptor.

Due to the potent CB_1 antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as dementia, distonia, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, as well as for the treatment of pain disorders and other CNS-diseases involving cannabinoid neurotransmission, and in the treatment of gastrointestinal disorders and cardiovascular disorders.

The affinity of the compounds of the invention for cannabinoid CB_1 receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabis CB_1 receptor is stably transfected in conjunction with [3H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid

scintillation counting.

The cannabinoid CB_1 antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB_1 receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB_1 receptors by CB_1 receptor agonists (*e.g.* CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB_1 receptor-mediated response can be antagonised by CB_1 receptor antagonists such as the compounds of the invention.

At least one centre of chirality is present (at the C_4 position of the 4,5-dihydro-1H-pyrazole moiety) in the compounds of the formula (I). The invention relates both to racemates, mixtures of diastereomers and the individual stereoisomers of the compounds having formula (I).
The invention also relates both to the E isomer, Z isomer and E/Z mixtures of compounds having formula (I) wherein Aa has the meaning (i) or (ii) as described herein above.

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

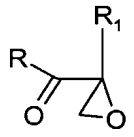
The compounds of the invention having formula (III) (*vide infra*), wherein R_2 represents hydrogen can be obtained according to methods known, for example: a) EP 0021506; b) DE 2529689.

A suitable synthesis for the compounds according to the present invention is the following:

Synthesis route A (for compounds having formula (I), wherein Aa has the meaning (i) or (ii) as described herein above).

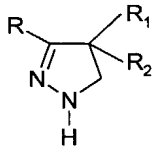
Step 1 of route A

Reaction of a compound having formula (II)



(II)

with hydrazine or hydrazine hydrate. This reaction gives a compound having formula (III)

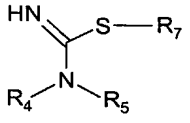


(III)

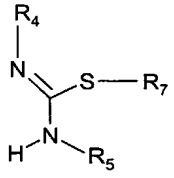
wherein R_2 represents a hydroxy group. This reaction is preferably carried out in a polar solvent, such as for example ethanol. Compounds having formula (III) wherein R_2 represents a hydroxy group and wherein R and R_1 have the meaning as described herein above for compound (I) are new.

Step 2 of route A

Reaction of a compound having formula (III) with a compound having formula (IVa) or a compound having formula (IVb)

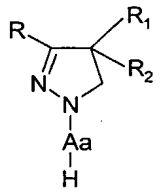


(IVa)



(IVb)

wherein R_7 represents a lower alkyl group, such as for example 2-methyl-2-thiopseudourea, or with a suitable salt form thereof in the presence of a base. This reaction gives a 4,5-dihydro-1H-pyrazole-1-carboxamidine derivative having formula (V)



(V)

wherein Aa has the meaning (i) or (ii) as described herein above. Compounds having formula (V) wherein Aa has the meaning (i) or (ii) as described herein above and wherein R, R_1 and R_2 have the meaning as described herein above for compound (I) are new.

Alternatively, a compound having formula (III) is reacted with a so-called guanylating agent. Examples of such guanylating agents are 1H-pyrazole-1-carboxamidine and its salts (for example the hydrochloride salt) and 3,5-dimethyl-1H-pyrazole-1-carboxamidine and its salts (for example the nitrate salt) and the like. This reaction gives a carboxamidine derivative having formula (V).

Alternatively, a compound having formula (III) is reacted with a so-called protected guanylating agent. Examples of such protected guanylating agents are N-(benzyloxycarbonyl)-1H-pyrazole-1-carboxamidine, N-(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and N,N'-bis-(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and the like. This reaction gives after deprotection a compound having formula (V).

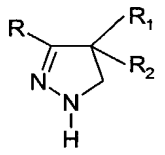
Step 3 of route A

The compound having formula (V) is reacted with an optionally substituted compound of the formula R_3-SO_2X or R_3-COX, wherein R_3 has the above mentioned meaning and X represents a halogen atom. This reaction is preferably carried out in the presence of a base, such as triethylamine in an aprotic solvent, such as acetonitrile. This reaction gives compound (I) wherein Bb represents a sulfonyl group or a carbonyl group, respectively.

Synthesis route A1 (for compounds having formula (I), wherein Aa has the meaning (i) or (ii) as described herein above)

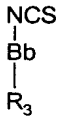
Step 1 of route A1

Reaction of a compound having formula (III)



(III)

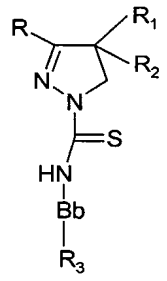
with a thioisocyanate derivative having formula (VI) .



(VI)

This reaction is preferably carried out in an inert organic solvent, such as for example acetonitrile.

This reaction gives a thiocarboxamide derivative having formula (VII). Compounds having formula (VII) wherein R, R_1, R_2, R_3 and Bb have the meaning as described herein above for compound (I) are new.



(VII)

Step 2 of route A1

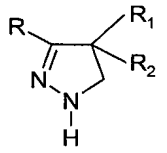
Reaction of a compound having formula (VII) with an amine in the presence of a mercury(II) salt, such as for example $HgCl_2$, gives a compound having formula (I) wherein Aa has the meaning (i) or (ii) as described herein above.

This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.

Synthesis route A2 (for compounds having formula (I), wherein Aa has the meaning (i) or (ii) as described herein above)

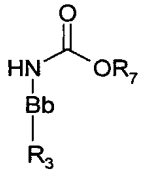
Step 1 of route A2

Reaction of a compound having formula III



(III)

with a carbamate ester derivative having formula (VIII).

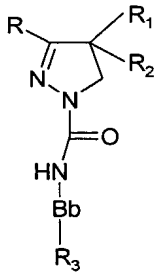


(VIII)

wherein R_7 represents a lower alkyl group, for example methyl.

This reaction is preferably carried out in an inert organic solvent, such as for example 1,4-dioxane.

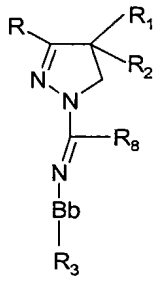
This reaction gives a 4,5-dihydropyrazole-1-carboxamide derivative having formula (IX). Compounds having formula (IX) wherein R, R_1, R_2, R_3 and Bb have the meaning as described herein above for compound (I) are new.



(IX)

Step 2 of route A2

Reaction of a compound having formula (IX) with a halogenating agent, such as for example PCl_5, gives a 4,5-dihydropyrazole-1-carboximidoyl halogenide derivative having formula (X)



(X)

wherein R_8 represents a halogen atom, such as for example chloro. This reaction is preferably carried out in an inert organic solvent, such as for example chlorobenzene.

Compounds having formula (X) wherein R, R_1, R_2, R_3 and Bb have the meaning as described herein above for compound (I) and wherein R_8 represents a halogen atom are new.

Step 3 of route A2

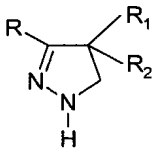
Reaction of a compound having formula (X) with an amine gives a compound having formula (I) wherein Aa has the meaning (i) or (ii) as described herein above.

This reaction is preferably carried out in an inert organic solvent, such as for example dichloromethane.

Synthesis route A3 (for compounds having formula (I), wherein Aa has the meaning (i) or (ii) as described herein above)

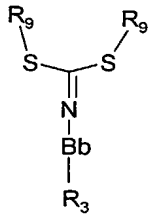
Step 1 of route A3

Reaction of a compound having formula III



(III)

with a dithioimidocarbonic ester derivative having formula (XI) .

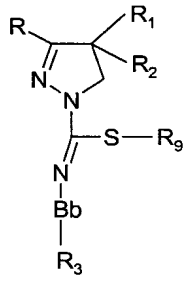


(XI)

wherein R_9 represents a C_{1-3} alkyl group.

This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.

This reaction gives a carboximidothioic ester derivative having formula (XII).



(XII)

wherein R_9 represents a C_{1-3} alkyl group. Compounds having formula (XII) wherein R, R_1, R_2, R_3 and Bb have the meaning as described herein above for compound (I) and wherein R_9 represents a C_{1-3} alkyl group are new.

Step 2 of route A3

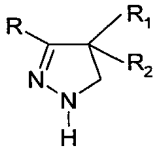
Reaction of a compound having formula (XII) with an amine gives a compound having formula (I) wherein Aa has the meaning (i) or (ii) as described herein above.

This reaction is preferably carried out in a polar organic solvent, such as for example methanol.

Synthesis route B (for compounds having formula (I), wherein Aa has the meaning (iii) or (iv) as described herein above)

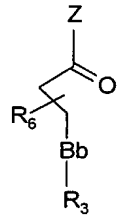
Step 1 of route B

Reaction of a compound having formula (III)

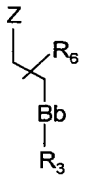


(III)

with a compound having formula (XIII), or a compound having formula (XIV), respectively



(XIII)



(XIV)

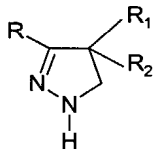
wherein Bb, R_3 and R_6 have the above mentioned meanings and Z represents a so-called leaving group.

These reactions give compounds having formula (I), wherein Aa has the meaning (iii) or (iv), respectively.

Synthesis route C (for compounds having formula (I), wherein Aa has the meaning (v) as described herein above)

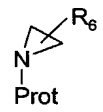
Step 1 of route C

Reaction of a compound having formula (III)

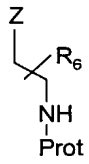


(III)

with an aziridine derivative having formula (XV), or a compound having formula (XVI), respectively



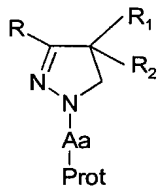
(XV)



(XVI)

wherein R_6 has the above mentioned meaning, Z represents a so-called leaving group and Prot represents a so-called protective group, such as *tert*-butoxycarbonyl, benzyloxycarbonyl and the like.

These reactions give compounds having formula (XVII)



(XVII)

wherein Aa has the meaning (v) as described herein above. Compounds having formula (XVII) wherein R, R_1 and R_2 have the meaning as described herein above for compound (I) and wherein Aa has the meaning (v) as described herein above and wherein Prot represents a so-called protective group are new.

Subsequent removal of the so-called protective group according to known methods (see for example: T.W. Greene, P.G.M. Wuts, "Protective Groups in Organic Synthesis", third edition, John Wiley & Sons, Inc., New York, 1999) gives compounds (V), wherein Aa has the meaning (v) as described herein above). Compounds having formula (V) wherein R, R_1 and R_2 have the meaning as described herein above for compound (I) and wherein Aa has the meaning (v) as described herein above are new.

Step 2 of route C

The compound having formula (V), wherein Aa has the meaning (v) as described herein above, is reacted with an optionally substituted compound of the formula R_3-SO_2X or R_3-COX, wherein R_3 has the above mentioned meaning and X is halogen. This reaction preferably is carried out in the presence of a base, such as triethylamine in an aprotic solvent, such as acetonitrile. This reaction gives compound (I) wherein Bb represents a sulfonyl group or carbonyl group respectively.

Alternatively, the above mentioned compound having formula (V) can be reacted with a compound of the formula R_3-COOH via formation of an active ester or in the presence of a so-called coupling reagent.

The preparation of the compounds is illustrated in the following examples.

Example I

3-(4-Chlorophenyl)-4,5-dihydro-4-hydroxy-4-phenyl-1H-pyrazole

2-(4-Chlorobenzoyl)-2-phenyloxirane (112 gram, 0.43 mol) is dissolved in ethanol (650 ml) at 35 °C. To the resulting stirred solution is added $N_2H_4.H_2O$ (42 ml) and the formed 3-(4-chlorophenyl)-4,5-dihydro-4-hydroxy-4-phenyl-1H-pyrazole slowly precipitates. After standing for 16 hours the crystalline material is collected by filtration and successively washed with ethanol, water and ethanol and

subsequently dried to give 3-(4-chlorophenyl)-4,5-dihydro-4-hydroxy-4-phenyl-1H-pyrazole (92 gram, 78 % yield). Melting point: 195-196 °C.

Example II

3-(4-Chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamidine

Part A: A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (5.13 gram, 20.0 mmol), 2-methyl-2-thiopseudourea hydroiodide (5.00 gram, 23.0 mmol) and pyridine (10 ml) is heated at 110 °C for 1 hour. After one night standing at room temperature diethyl ether is added and the precipitate is collected by filtration. This precipitate is washed three times with diethyl ether portions to afford a solid (9 gram). Melting point: ~230 °C. This solid is dissolved in methanol (20 ml). To the resulting solution is successively added a 2N sodium hydroxide solution (12 ml) and water (200 ml). The formed precipitate is collected by filtration, washed two times with diethyl ether and successively with diisopropyl ether. The resulting solid is dried *in vacuo* to yield 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (5.1 gram, 88 % yield). Melting point: 187-189 °C.

Part B: To a stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (0.50 gram, 1.68 mmol) and 4-fluorophenylsulfonyl chloride (0.34 gram, 1.75 mmol) in acetonitrile (10 ml) is added N,N-dimethyl-4-aminopyridine (0.020 gram, 0.175 mmol) and triethylamine (1 ml). The resulting solution is stirred at room temperature for 30 minutes. After addition of a 2N sodium hydroxide solution and extraction with ethylacetate (400 ml), the ethylacetate layer is concentrated *in vacuo*. The resulting crude residue is further purified by means of flash chromatography (petroleum ether/diethyl ether = 1/1 (v/v), followed by ethylacetate). Subsequent concentration *in vacuo* affords solid 3-(4-chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamidine (0.55 gram, 72 % yield). Melting point: 214-215 °C

In an analogous manner the compounds having formula (I) listed below have been prepared:

4,5-Dihydro-N-((4-fluorophenyl)sulfonyl)-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamidine: Melting point: 155-156 °C

4,5-Dihydro-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-N-((4-methoxyphenyl)sulfonyl)-1H-pyrazole-1-carboxamidine: Melting point: 148-150 °C

3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-N-((2,4,6-trimethylphenyl)sulfonyl)-1H-pyrazole-1-carboxamidine: Melting point: 221-222 °C
3-(4-Chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-hydroxy-4-phenyl-1H-pyrazole-1-carboxamidine: Melting point: 227-228 °C

Example III

3-(4-Chlorophenyl)-4,5-dihydro-N-(1-naphtoyl)-4-phenyl-1H-pyrazole-1-carboxamidine

To a stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (0.75 gram, 2.50 mmol) and 1-naphtoyl chloride (0.4 ml, 2.70 mmol) in acetonitrile (15 ml) is added triethylamine (1ml). The resulting mixture is stirred at room temperature for 1 hour. After addition of a 2N sodium hydroxide solution and extraction with ethylacetate, the ethylacetate layer is concentrated *in vacuo*. The resulting crude residue is further purified by means of flash chromatography (petroleum ether/diethyl ether = 3/1 (v/v), followed by ethylacetate). Subsequent concentration *in vacuo* affords 3-(4-chlorophenyl)-4,5-dihydro-N-(1-naphtoyl)-4-phenyl-1H-pyrazole-1-carboxamidine (0.94 gram, 83 % yield). Melting point: 206-207 °C

In an analogous manner the compound having formula (I) listed below has been prepared:
3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-N-(2-pyridoyl)-1H-pyrazole-1-carboxamidine. Melting point: 118 °C (decomposition)

Example IV

N^1,N^1-Dimethyl-N^2-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

Part A: A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol), [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester (CAS: 13068-12-7) (9.20 gram, 31.1 mmol) and triethylamine (15 ml) in acetonitrile (200 ml) is heated at reflux temperature for 20 hours. An additional portion of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol) is added and the resulting mixture is heated at reflux temperature for another 16 hours. After concentration *in vacuo,* dichloromethane is added and the resulting solution is washed twice with water and dried over anhydrous Na_2SO_4. After filtration and evaporation *in vacuo* the residue is further purified by flash chromatography (diethyl ether/ petroleum ether = 1/1 (v/v)) to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-

pyrazole-1-carboximidothioic acid methyl ester (12.5 gram, 80% yield based on [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester) as an amorphous solid.

Part B: To a stirred mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidothioic acid methyl ester (4.20 gram, 8.30 mmol) in methanol (75 ml) is added dimethylamine (10 ml) and dichloromethane (75 ml) and the resulting solution is stirred at room temperature for 6 hours. Evaporation *in vacuo* and subsequent flash chromatographic purification (diethyl ether/ petroleum ether = 1/1 (v/v), followed by diethyl ether) gives a solid which is further purified by recrystallisation from diisopropyl ether to yield N^1,N^1-dimethyl-N^2-((4-chloro-phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-
1-carboxamidine (2.63 gram, 63 % yield). Melting point: 182 °C.

In an analogous manner the compounds having formula (I) listed below have been prepared:
N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(3-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 101-105 °C.
N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(4-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 112-115 °C.
N^1,N^1-Dimethyl-N^2-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-hydroxy-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
N-Ethyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-hydroxy-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 183-185 °C..

Example V

N-Methyl-N'-(3-(trifluoromethyl)benzoyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

Part A: To 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (5.13 gram, 20.0 mmol) in acetonitrile (80 ml) is added 3-(trifluoromethyl)benzoylisothio-cyanate (4.62 gram, 20.0 mmol) at 0 °C and the resulting mixture is stirred for 1 hour. The formed yellow precipitate is collected by filtration and washed with a small portion of acetonitrile and water, respectively, and subsequently dried *in vacuo* to give 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-N-((3-trifluoromethyl) benzoyl)-1H-pyrazole-1-thiocarboxamide (8.26 gram, 85 % yield). Melting point: 180-182 °C.

Part B: To a stirred suspension of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-N-((3-trifluoromethyl)benzoyl)-1H-pyrazole-1-thiocarboxamide (4.88 gram, 10.0 mmol) in acetonitrile (50 ml) is added cold methylamine (5 ml) to give a green solution. After addition of a solution of $HgCl_2$ (3.0 gram, 11 mmol) in 25 ml acetonitrile, the resulting mixture is stirred for three hours. The precipitate is removed by filtration over hyflo and the filtrate is collected and concentrated *in vacuo*. After addition of ethylacetate and 0.5 N NaOH, the ethylacetate layer is collected, washed with saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Chromatography (dichloromethane/acetone = 9/1 (v/v)) gives N-methyl-N'-(3-(trifluoro-methyl)benzoyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (0.99 gram, 20 % yield) as a foam. Melting point: Amorphous. R_f (Silicagel: Dichloromethane/acetone = 9/1 (v/v)) = 0.3.

Example VI

N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

Part A: To a solution of N-((4-chlorophenyl)sulfonyl)carbamic acid methyl ester (CAS: 34543-04-9) (2.99 gram, 12.0 mmol) and pyridine (4 ml) in 1,4-dioxane (20 ml) is added 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (3.39 gram, 13.2 mmol) and the resulting mixture is stirred for 4 hours at 100 °C. After concentration *in vacuo* the residue is dissolved in dichloromethane, successively washed with water, 1N HCl and water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to a volume of 20 ml. Methyl-tert-butyl ether (60 ml) is added and the resulting solution is concentrated to a volume of 20 ml. The formed crystals are collected by filtration and recrystallised from methyl-*tert*-butyl ether to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (4.75 gram, 76 % yield) Melting point: 211-214 °C.

Part B: A mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (3.67 gram, 7.75 mmol) and phosphorus pentachloride (1.69 gram, 8.14 mmol) in chlorobenzene (40 ml) is heated at reflux for 1 hour. After thorough concentration *in vacuo*, the formed N-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidoyl chloride is suspended in dichloromethane and reacted with cold methylamine (1.5 ml). After stirring at room temperature for 1 hour, the mixture is concentrated *in vacuo*. The residue is crystallised from diethyl ether to give

N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (2.29 gram, 61 % yield). Melting point: 96-98 °C (dec.).

In an analogous manner the compounds having formula (I) listed below have been prepared:

N-Methyl-N'-((3-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl - 1H-pyrazole-1-carboxamidine. Melting point: 156-160 °C.

N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(5-chloro-2-thienyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous

N-Propyl-N'-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 129-138 °C.

N-(2-Propyl)-N'-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 110-112 °C.

N-Methyl-N'-((2-propyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.

N-(2-Propyl)-N'-((4-chlorophenyl)sulfonyl)-3-(4-pyridyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.

N^1-Ethyl-N^1-methyl-N^2-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 184 °C.

N^1-Ethyl-N^1-methyl-N^2-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 173-176 °C.

N^1,N^1-Dimethyl-N^2-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 195-196 °C.

N^1,N^1-Dimethyl-N^2-((3-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 195-198 °C.

N^1,N^1-Dimethyl-N^2-((3-methoxyphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 204-206 °C.

N-Ethyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.

N-Dimethylamino-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 155-159 °C.

N-Methyl-N'-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.

N^1,N^1-Dimethyl-N^2-((2-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point:148-151 °C.

N-Methyl-N'-((2,4-difluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 85 °C.

N-Acetamido-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
N-(2,2,2-Trifluoroethyl)-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
N-(2-Pyridyl)-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 142-146 °C.
N-(4-Pyridyl)-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 204-206 °C.
N-Phenyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 158-160 °C.

Example VII

3-(4-Chlorophenyl)-1-[3-((4-chlorophenyl)sulfonyl)butanoyl]-4,5-dihydro-4-phenyl-1H-pyrazole

To a stirred mixture of 3-((4-chlorophenyl)sulfonyl)butyric acid (1.85 gram, 7.00 mmol), diisopropylethylamine (3 ml) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.50 gram, 15.7 mmol) was added 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (3.00 gram, 11.7 mmol) and the resulting mixture was stirred for 16 hours at room temperature. After concentration *in vacuo* the resulting residue was purified by flash chromatography (petroleum ether/ diethyl ether = 1/2 (v/v), followed by diethyl ether) to give 3-(4-chlorophenyl)-1-[3-((4-chlorophenyl)sulfonyl)butanoyl]-4,5-dihydro-4-phenyl-1H-pyrazole (3.69 gram, 63 % yield) as a diastereomeric mixture. Melting point: amorphous

In an analogous manner the compounds having formula (I) listed below have been prepared:
3-(4-Chlorophenyl)-1-[3-(phenylsulfonyl)propanoyl]-4,5-dihydro-4-phenyl-1H-pyrazole. Melting point: 122-123 °C.
3-(4-Chlorophenyl)-1-[3-((4-chlorophenyl)sulfonyl)propanoyl]-4,5-dihydro-4-phenyl-1H-pyrazole. Melting point: 178-181 °C.

Example VIII

3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-1-[2-((3-(trifluoromethyl)phenyl)-sulfonyl)ethyl]-1H-pyrazole

To a stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (1.7 gram, 6.60 mmol) and collidine (2 ml) in acetonitrile (25 ml) is slowly added a solution of 2-((3-(trifluoromethyl)phenyl)sulfonyl)ethyl chloride (1.5 gram, 5.50 mmol) in acetonitrile (20 ml) and the resulting solution is heated at reflux

temperature for 16 hours. After concentration *in vacuo* the residue is dissolved in ethylacetate and washed with aqueous sodium hydrogencarbonate solution. The resulting ethylacetate layer is successively washed with 1N hydrochloric acid solution and aqueous sodium hydrogencarbonate solution.

Subsequent flash chromatographic purification (petroleum ether/ diethyl ether = 1/2 (v/v)) gives an oil which is crystallised from diisopropyl ether to afford 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1-[2-((3-(trifluoromethyl)phenyl)sulfonyl)ethyl]-1H-pyrazole (0.52 gram, 19 % yield). Melting point: 118-119 °C.

In an analogous manner the compounds having formula (I) listed below have been prepared:

3-(4-Chlorophenyl)-1-[2-(benzylsulfonyl)ethyl]-4,5-dihydro-4-phenyl-1H-pyrazole. Melting point: 161 °C.

3-(4-Chlorophenyl)-1-[2-((4-chlorophenyl)sulfonyl)ethyl]-4,5-dihydro-4-phenyl-1H-pyrazole. Melting point: Amorphous

3-(4-Chlorophenyl)-1-[2-((4-chlorophenyl)sulfonyl)ethyl]-4,5-dihydro-4-hydroxy-4-phenyl-1H-pyrazole. Melting point: 127-128 °C.

Example IX

N-[2-(3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazol-1-yl)ethyl]-3-(trifluoromethyl)benzenesulfonamide

Part A: A stirred solution of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (5.00 gram, 19.5 mmol) and N-(*tert*-butoxycarbonyl)aziridine (2.00 gram, 14.0 mmol) in toluene (100 ml) is heated at reflux temperature for 16 hours. After concentration *in vacuo* the residue is purified by flash chromatography (petroleum ether/ diethyl ether = 3/1 (v/v)), followed by petroleum ether/ diethyl ether = 1/1 (v/v)). After concentration *in vacuo* the remaining oily residue is crystallised from diisopropyl ether to afford 1-[2-((*tert*-butoxycarbonyl)amino)ethyl]-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (1.91 gram, 34 %). Repeated crystallisations from the mother liquor afforded an additional amount of crystalline 1-[2-((*tert*-butoxycarbonyl)amino)ethyl]-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (1.19 gram).

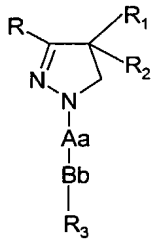
Part B: To a solution of 1-[2-((*tert*-butoxycarbonyl)amino)ethyl]-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (1.91 gram, 4.8 mmol) in dichloromethane (50 ml) is added trifluoroacetic acid (5 ml) and the resulting solution is stirred at room temperature for 5 hours. After concentration *in vacuo* the residue is dissolved in ethylacetate and washed with 2N sodium hydroxide solution. The ethyl acetate layer is dried over magnesium sulfate, filtered and

concentrated *in vacuo* to afford 1-(2-aminoethyl)-3-(4-chlorophenyl)- 4,5-dihydro-4-phenyl-1H-pyrazole (1.44 gram, quantitative yield) as an oil.

Part C: To a solution of 1-(2-aminoethyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (0.56 gram, 1.87 mmol) and diisopropylethylamine in acetonitrile (20 ml) is added 3-(trifluoromethyl)phenylsulfonyl chloride (0.35 ml, 2.18 mmol) and the resulting solution is stirred at room temperature for 20 minutes. After concentration *in vacuo* the residue is dissolved in ethylacetate and washed with 2N sodium hydroxide solution. The ethylacetate layer is concentrated *in vacuo.* The resulting oil is crystallised from a small amount of diisopropyl ether to afford crystalline N-[2-(3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazol-1-yl)ethyl]-3-(trifluoromethyl)benzenesulfonamide (0.44 gram, 46 % yield). Melting point: 94-96 °C.

Claims

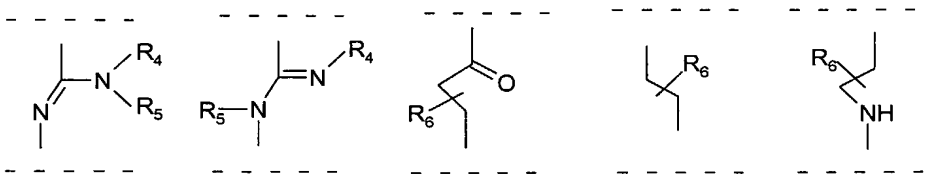
1. A compound of formula (I)



(I)

wherein

- R and R_1 are the same or different and represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group C_{1-3}-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C_{1-2})-amino, mono- or dialkyl (C_{1-2})-amido, (C_{1-3})-alkyl sulfonyl, dimethylsulfamido, C_{1-3}-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R_1 represent naphtyl,
- R_2 represents hydrogen, hydroxy, C_{1-3}-alkoxy, acetyloxy or propionyloxy,
- Aa represents one of the groups (i), (ii), (iii), (iv) or (v)



(i) (ii) (iii) (iv) (v)

wherein

- R_4 and R_5 independently of each other represent hydrogen or C_{1-8} branched or unbranched alkyl or C_{3-8} cycloalkyl or R_4 represents acetamido or dimethylamino or 2,2,2-trifluoroethyl or phenyl or pyridyl with the proviso that R_5 represents hydrogen
- R_6 represents hydrogen or C_{1-3} unbranched alkyl

- Bb represents sulfonyl or carbonyl,
- R_3 represents benzyl, phenyl, thienyl or pyridyl which may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, or R_3 represents C_{1-8} branched or unbranched alkyl or C_{3-8} cycloalkyl, or R_3 represents naphtyl

and tautomers, prodrugs and salts thereof.

2. A compound having formula (I) as claimed in claim 1, wherein R is the group 4-chlorophenyl, R_1 is phenyl, R_2 is hydrogen, Aa is the group (i) wherein R_4 is hydrogen and R_5 is methyl, Bb is sulfonyl, and R_3 represents 4-chlorophenyl, and salts thereof.

3. A pharmaceutical composition containing at least one compound as claimed in 1 as an active component.

4. A method of preparing pharmaceutical compositions characterized in that a compound as claimed in claim 1 is brought in a form suitable for administration.

5. Process for the preparation of compounds having formula I, characterized in that

a) a compound is prepared wherein R, R_1-R_3 and Bb have the meanings given in claim 1 and Aa is a group of the formula (i) or (ii) as defined in claim 1 by

1) reacting a compound having formula (II) with hydrazine or hydrazine hydrate to obtain a compound having formula (III), which is reacted with a compound having formula (IVa) of (IVb) to give a compound having formula (V), which is reacted with a compound of the formula R_3-SO_2X or R_3-COX, wherein X is halogen, or

2) reacting a compound having formula (III) with a thioisocyanate of the formula (VI) to produce a compound of the formula (VII), which is reacted with an amine in the presence of a mercury (II) salt, or

3) reacting a compound having formula (III) with a compound of the formula

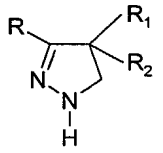
(VIII) to give a compound of the formula (IX) which is reacted with a halogenating agent to give a compound having formula (X) which is reacted with an amine, or

4) reacting a compound having formula (III) with a compound of the formula (XI) to give a compound having formula (XII) which is reacted with an amine, or

b) a compound is prepared wherein R, R_1-R_3 and Bb have the meanings given in claim 1 and Aa is a group of the formula (iii) or (iv) as defined in claim 1 by reacting a compound of the formula (III) with a compound of the formula (XIII) of (XIV), or

c) a compound is prepared wherein R, R_1-R_3 and Bb have the meanings given in claim 1 and Aa is a group of the formula (v) as defined in claim 1, by reacting a compound having formula (III) with a compound having formula (XV) or (XVI) to give a compound having formula (XVII), which is deprotected to give a compound having formula (V), which is reacted with a compound having formula R_3-SO_2X or R_3-COX wherein X is halogen or with a compound of the formula R_3-COOH.

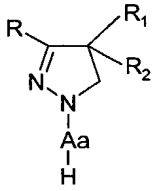
6. A compound of formula (III)



(III)

wherein R_2 represents a hydroxy group and wherein R and R_1 have the meanings given in claim 1.

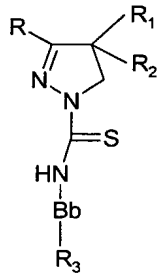
7. A compound of formula (V)



(V)

wherein Aa has the meaning (i), (ii) or (v) as given in claim 1 and wherein R, R_1 and R_2 have the meanings given in claim 1.

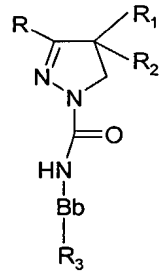
8. A compound of formula (VII)



(VII)

wherein R, R_1, R_2 R_3 and Bb have the meanings given in claim 1.

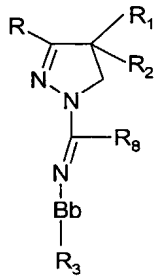
9. A compound of formula (IX)



(IX)

wherein R, R_1, R_2 R_3 and Bb have the meanings given in claim 1.

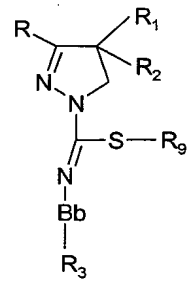
10. A compound of formula (X)



(X)

wherein R, R_1, R_2 R_3 and Bb have the meanings given in claim 1 and wherein R_8 represents a halogen atom.

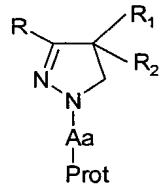
11. A compound of formula (XII)



(XII)

wherein R, R_1, R_2, R_3 and Bb have the meanings given in claim 1 and wherein R_9 represents a C_{1-3} alkyl group.

12. A compound of formula (XVII)



(XVII)

wherein R, R_1 and R_2 have the meanings given in claim 1 and wherein Aa has the meaning (v) as given in claim 1 and wherein Prot represents a so-called protective group.

13. A method of treating psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as Parkinson's disease, dementia, distonia, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, ischaemia, pain and other CNS-diseases involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

14. A method of treating gastrointestinal disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

15. A method of treating cardiovascular disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

INTERNATIONAL SEARCH REPORT

Inte[illegible]al Application No
PCT/EP 01/03247

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/06 C07D409/04 C07D401/04 A61K31/415 A61P25/04
A61P9/00 C07D231/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 624 941 A (BARTH FRANCIS ET AL) 29 April 1997 (1997-04-29) abstract	1,13-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 2001	25/05/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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